

Sub A'

What is claimed is:

1. A compound wherein a residue of a compound of formula I (Figure 1) is linked directly or by a linker to a residue of one or more chemotherapeutic agents; wherein X is CN, OH, CH₃, or adenosyl; or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1 wherein a residue of a chemotherapeutic agent is directly linked to a residue of the b, d or e-carboxamide of the compound of formula I.
3. The compound of claim 1 wherein a residue of a chemotherapeutic agent is linked by a linker to a residue of the b-, d- or e-carboxamide of the compound of formula I.
4. The compound of claim 1 wherein a residue of a chemotherapeutic agent is directly linked to the b-carboxamide of the compound of formula I.
5. The compound of claim 1 wherein a residue of a chemotherapeutic agent is linked by a linker to a residue of the b-carboxamide of the compound of formula I.
6. The compound of claim 1 wherein a residue of a chemotherapeutic agent is directly linked to a residue of the d-carboxamide of the compound of formula I.
7. The compound of claim 1 wherein a residue of a chemotherapeutic agent is linked by a linker to a residue of the d-carboxamide of the compound of formula I.

8. The compound of claim 1 wherein a residue of a chemotherapeutic agent is directly linked to a residue of the e-carboxamide of the compound of formula I.

9. The compound of claim 1 wherein a residue of a chemotherapeutic agent is linked by a linker to a residue of the e-carboxamide of the compound of formula I.

10. The compound of claim 1 wherein a residue of a first chemotherapeutic agent is linked directly or by a linker to a residue of the b-carboxamide of the compound of formula I and a residue of a second chemotherapeutic agent is linked directly or by a linker to a residue of the d-carboxamide of the compound of formula I.

11. The compound of claim 1 wherein a residue of a first chemotherapeutic agent is linked by a linker to a residue of the b-carboxamide of the compound of formula I and a residue of a second chemotherapeutic agent is linked by a linker to a residue of the d-carboxamide of the compound of formula I.

12. The compound of claim 1 wherein the chemotherapeutic agent is an antineoplastic agent.

13. The compound of claim 12 wherein the antineoplastic agent is a cytotoxic agent.

14. The compound of claim 13 wherein the cytotoxic agent is doxorubicin or paclitaxel.

Sub A

15. The compound of any one of claims 1, 3, 5, 7, 9, 10, and 11 wherein at least one linker is of the formula W-A-Q wherein A is (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, or (C_6-C_{10})aryl, wherein W and Q are each independently -N(R)C(=O)-, -C(=O)N(R)-, -OC(=O)-, -C(=O)O-, -O-, -S-, -S(O)-, -S(O)₂-, -N(R)-, -C(=O)-, or a direct bond; wherein each R is independently H or (C_1-C_6)alkyl.

16. The compound of claim 15 wherein W and Q are each -N(R)-.

Sub A 3

17. The compound of any one of claims 1, 3, 5, 7, 9, 10, and 11 wherein at least one linker is of the formula W-(CH_2)_n-Q wherein, n is between about 1 and about 20, between about 1 and about 15, between about 2 and about 10, between about 2 and about 6, or between about 4 and about 6; wherein W and Q are each independently -N(R)C(=O)-, -C(=O)N(R)-, -OC(=O)-, -C(=O)O-, -O-, -S-, -S(O)-, -S(O)₂-, -C(=O)-, -N(R)-, or a direct bond; wherein each R is independently H or (C_1-C_6)alkyl.

18. The compound of claim 17 wherein at least one of W and Q is -N(R)-.

19. The compound of claim 18 wherein n is in the range from about 2 to about 6, inclusive.

Sub A 4

20. The compound of any one of claims 1, 3, 5, 7, 9, 10, and 11 wherein the linker is a divalent radical formed from a peptide or an amino acid.

21. The compound of claim 20 wherein the peptide comprises 2 to about 25 amino acids.

22. The compound of claim 20 wherein the peptide is poly-L-lysine, containing about 8 to about 11 residues.

23. The compound of any one of claims 1, 3, 5, 7, 9, 10, and 11 wherein the linker is a 1,ω-divalent radical formed from a peptide.

24. The compound of any one of claims 1, 3, 5, 7, 9, 10, and 11 wherein the linker separates the residue of a compound of formula I from the residue of the chemotherapeutic agent by about 5 angstroms to about 50 angstroms.

b6 b7 b8 b9 b10 b11
25. A compound wherein a residue of a compound of formula I is linked directly or by a linker to a residue of a chemotherapeutic agent through the 6-position and wherein a residue of the compound of formula I is linked directly or by a linker to a residue of one or more additional chemotherapeutic agents; or a pharmaceutically acceptable salt thereof.

26. The compound of claim 25 wherein a residue of a chemotherapeutic agent is directly linked to a residue of the b-, d- or e-carboxamide of the compound of formula I.

27. The compound of claim 25 wherein a residue of a chemotherapeutic agent is linked by a linker to a residue of the b-, d- or e-carboxamide of the compound of formula I.

28. The compound of claim 25 wherein a residue of a chemotherapeutic agent is directly linked to the b-carboxamide of the compound of formula I.

29. The compound of claim 25 wherein a residue of a chemotherapeutic agent is linked by a linker to a residue of the b-carboxamide of the compound of formula I.

30. The compound of claim 25 wherein a residue of a chemotherapeutic agent is directly linked to a residue of the d-carboxamide of the compound of formula I.

31. The compound of claim 25 wherein a residue of a chemotherapeutic agent is linked by a linker to a residue of the d-carboxamide of the compound of formula I.

32. The compound of claim 25 wherein a residue of a chemotherapeutic agent is directly linked to a residue of the e-carboxamide of the compound of formula I.

33. The compound of claim 25 wherein a residue of a chemotherapeutic agent is linked by a linker to a residue of the e-carboxamide of the compound of formula I.

34. The compound of claim 25 wherein a residue of a chemotherapeutic agent is linked directly or by a linker to a residue of the b-carboxamide of the compound of formula I and a residue of a second chemotherapeutic agent is linked directly or by a linker to a residue of the d-carboxamide of the compound of formula I.

35. The compound of claim 25 wherein a residue of a chemotherapeutic agent is linked by a linker to a residue of the b-carboxamide of the compound of formula I and a residue of a second chemotherapeutic agent is linked by a linker to a residue of the d-carboxamide of the compound of formula I.

Sub A^b

36. The compound of any one of claims 25, 27, 29, 31, 33, 34 and 35 wherein at least one linker is of the formula W-A-Q wherein A is (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_3-C_8) cycloalkyl, or (C_6-C_{10}) aryl, wherein W and Q are each independently $-N(R)C(=O)-$, $-C(=O)N(R)-$, $-OC(=O)-$, $-C(=O)O-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-N(R)-$, $-C(=O)-$, or a direct bond; wherein each R is independently H or (C_1-C_6) alkyl.

37. The compound of claim 36 wherein at least one of W and Q is $-N(R)-$.

Sub A^a

38. The compound of any one of claims 25, 27, 29, 31, 33, 34 and 35 wherein at least one linker is of the formula W- $(CH_2)_n$ -Q wherein, n is between about 1 and about 20, between about 1 and about 15, between about 2 and about 10, between about 2 and about 6, or between about 4 and about 6; wherein W and Q are each independently $-N(R)C(=O)-$, $-C(=O)N(R)-$, $-OC(=O)-$, $-C(=O)O-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-C(=O)-$, $-N(R)-$, or a direct bond; wherein each R is independently H or (C_1-C_6) alkyl.

39. The compound of claim 38 wherein at least one of W and Q is $-N(R)-$.

Sub a⁹

40. The compound of claim 38 wherein n is in the range of about 2 to about 6, inclusive.

Sub a⁹

41. The compound of any one of claims 25, 27, 29, 31, 33, 34 and 35 wherein a linker is a divalent radical formed from a peptide or an amino acid.

42. The compound of claim 41 wherein the peptide comprises 2 to about 25 amino acids.

43. The compound of claim 42 wherein the peptide is poly-L-lysine, containing about 8 to about 11 residues.

44. The compound of any one of claims 25, 27, 29, 31, 33, 34 and 35 wherein the linker is a 1,ω-divalent radical formed from a peptide.

Sub a⁹

45. The compound of any one of claims 25, 27, 29, 31, 33, 34 and 35 wherein the linker separates the residue of a compound of formula I from the residue of the chemotherapeutic agent by about 5 angstroms to about 50 angstroms.

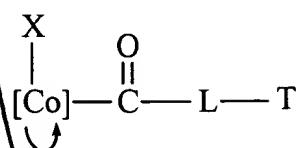
46. The compound of claim 25 wherein the chemotherapeutic agent is an antineoplastic agent.

47. The compound of claim 46 wherein the antineoplastic agent is a cytotoxic agent.

48. The compound of claim 47 wherein the cytotoxic agent is doxorubicin or paclitaxel.

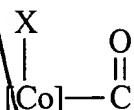
49.

A compound of formula II



(II)

wherein



is a residue of the compound of formula I;

X is CN, OH, CH₃, adenosyl, or LL-TT wherein LL is a linker or is absent and TT is a residue of a chemotherapeutic agent;

L is a linker or absent; and

T is a residue of a chemotherapeutic agent; or a pharmaceutically acceptable salt thereof.

50. The compound of claim 49 wherein L and LL are each independently of the formula W-A-Q wherein A is (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₈)cycloalkyl, or (C₆-C₁₀)aryl, wherein W and Q are each independently -N(R)C(=O)-, -C(=O)N(R)-, -OC(=O)-, -C(=O)O-, -O-, -S-, -S(O)-, -S(O)₂-, -N(R)-, -C(=O)-, or a direct bond; wherein each R is independently H or (C₁-C₆)alkyl.

51. The compound of claim 50 wherein at least one of W and Q is -N(R)-.

52. The compound of claim 49 wherein L and LL are each independently of the formula W-(CH₂)_n-Q wherein, n is between about 1 and about 20, between about 1 and about 15, between about 2 and about 10, between about 2 and about 6, or between about 4 and about 6; wherein W and Q are each independently -N(R)C(=O)-, -C(=O)N(R)-, -OC(=O)-, -C(=O)O-, -O-, -S-, -S(O)-, -S(O)₂-, -C(=O)-, -N(R)-, or a direct bond; wherein each R is independently H or (C₁-C₆)alkyl.

53. The compound of claim 52 wherein at least one of W and Q is -N(R)-.

54. The compound of claim 52 wherein n is between about 2 and about 6.

55. The compound of claim 49 wherein L separates T and the residue by about 5 angstroms to about 200 angstroms.

56. The compound of claim 49 wherein at least one of L and LL is a divalent radical formed from a peptide or an amino acid.

57. The compound of claim 56 wherein the peptide comprises 2 to about 25 amino acids.

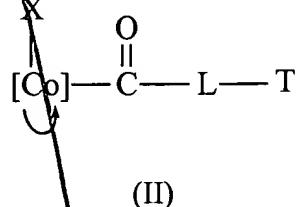
58. The compound of claim 56 wherein the peptide is poly-L-lysine, containing about 8 to about 11 residues.

59. The compound of claim 49 wherein at least one of L and LL is a 1,ω-divalent radical formed from a peptide or an amino acid.

60. The compound of claim 49 wherein at least one of T and TT is a residue of paclitaxel or doxorubicin, or a pharmaceutically acceptable salt thereof.

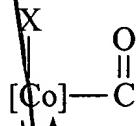
61. The compound of claim 49 wherein the (C=O) in the group is attached to L-T at the b-, d- or e- position.

62. A compound of formula II



(II)

wherein



is a residue of the compound of formula I;

X is LL-TT wherein LL is a linker or is absent and TT is a residue of a chemotherapeutic agent;

L is a linker or absent; and

T is a residue of a chemotherapeutic agent; or a pharmaceutically acceptable salt thereof.

63. The compound of claim 62 wherein L and LL are each independently of the formula W-A-Q wherein A is $(\text{C}_1\text{—C}_6)\text{alkyl}$, $(\text{C}_2\text{—C}_6)\text{alkenyl}$,

(C₂-C₆)alkynyl, (C₃-C₈)cycloalkyl, or (C₆-C₁₀)aryl, wherein W and Q are each independently -N(R)C(=O)-, -C(=O)N(R)-, -OC(=O)-, -C(=O)O-, -O-, -S-, -S(O)-, -S(O)₂-, -N(R)-, -C(=O)-, or a direct bond; wherein each R is independently H or (C₁-C₆)alkyl.

64. The compound of claim 63 wherein at least one of W and Q is -N(R)-.

65. The compound of claim 62 wherein L and LL are each independently of the formula W-(CH₂)_n-Q wherein, n is between about 1 and about 20, between about 1 and about 15, between about 2 and about 10, between about 2 and about 6, or between about 4 and about 6; wherein W and Q are each independently -N(R)C(=O)-, -C(=O)N(R)-, -OC(=O)-, -C(=O)O-, -O-, -S-, -S(O)-, -S(O)₂-, -C(=O)-, -N(R)-, or a direct bond; wherein each R is independently H or (C₁-C₆)alkyl.

66. The compound of claim 65 wherein at least one of W and Q is -N(R)-.

67. The compound of claim 65 wherein n is between about 2 and about 6.

68. The compound of claim 62 wherein L separates T and the residue by about 5 angstroms to about 200 angstroms.

69. The compound of claim 62 wherein at least one of L and LL is a divalent radical formed from a peptide or an amino acid.

70. The compound of claim 69 wherein the peptide comprises 2 to about 25 amino acids.

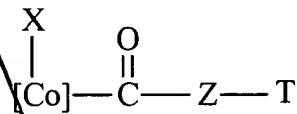
71. The compound of claim 69 wherein the peptide is poly-L-lysine, containing about 8 to about 11 residues.

72. The compound of claim 62 wherein at least one of L and LL is a 1,ω-divalent radical formed from a peptide.

73. The compound of claim 62 wherein at least one of T and TT is a residue of paclitaxel or doxorubicin, or a pharmaceutically acceptable salt thereof.

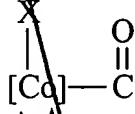
74. The compound of claim 62 wherein (C=O) in the group is attached to L-T is attached at the b-, d- or e- position.

75. A compound of formula III:



(III)

wherein



X is CN, OH, CH₃, adenosyl, or ZZ-TT wherein ZZ is a linker or is absent and TT is a residue of a chemotherapeutic agent;

and

*Sub 12
with*
T is a residue of a chemotherapeutic agent; or a pharmaceutically acceptable salt thereof.

76. The compound of claim 75 wherein Z and ZZ are each independently of the formula W-A-Q wherein A is (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, or (C_6-C_{10})aryl, wherein W and Q are each independently -N(R)C(=O)-, -C(=O)N(R)-, -OC(=O)-, -C(=O)O-, -O-, -S-, -S(O)-, -S(O)₂-, -N(R)-, -C(=O)-, or a direct bond; wherein each R is independently H or (C_1-C_6)alkyl.

77. The compound of claim 76 wherein at least one of W and Q is -N(R)-.

78. The compound of claim 75 wherein Z and ZZ are each independently of the formula W-(CH_2)_n-Q wherein, n is between about 1 and about 20, between about 1 and about 15, between about 2 and about 10, between about 2 and about 6, or between about 4 and about 6; wherein W and Q are each independently -N(R)C(=O)-, -C(=O)N(R)-, -OC(=O)-, -C(=O)O-, -O-, -S-, -S(O)-, -S(O)₂-, -C(=O)-, -N(R)-, or a direct bond; wherein each R is independently H or (C_1-C_6)alkyl.

79. The compound of claim 78 wherein at least one of W and Q is -N(R)-.

80. The compound of claim 78 wherein n is between about 2 and about 6.

81. The compound of claim 75 wherein Z separates T and the residue by about 5 angstroms to about 200 angstroms.

82. The compound of claim 75 wherein at least one of Z and ZZ is a divalent radical formed from a peptide or an amino acid.

83. The compound of claim 82 wherein the peptide comprises 2 to about 25 amino acids.

84. The compound of claim 75 wherein the peptide is poly-L-lysine, containing about 8 to about 11 residues.

85. The compound of claim 75 wherein at least one of Z and ZZ is a 1, ω -divalent radical formed from a peptide.

86. The compound of claim 75 wherein the (C=O) in the group is attached to Z-T at the b-, d- or e- position.

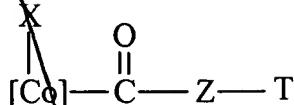
87. The compound of claim 75 wherein at least one of T and TT is a residue of an antineoplastic agent.

88. The compound of claim 87 wherein the antineoplastic agent is a cytotoxic agent.

89. The compound of claim 88 wherein the cytotoxic agent is doxorubicin or paclitaxel.

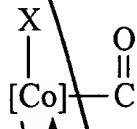
90.

A compound of formula III:



(III)

wherein



is a residue of the compound of formula I;

X is LL-TT wherein LL is a linker or is absent and TT is a residue of a chemotherapeutic agent;

Z is -N(R)-, -O-, or -S-, wherein R is H, (C_1-C_6)alkyl, or absent; and

T is a residue of a chemotherapeutic agent; or a pharmaceutically acceptable salt thereof.

91.

The compound of claim 90 wherein Z and ZZ are each independently of the formula W-A-Q wherein A is (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, or (C_6-C_{10})aryl, wherein W and Q are each independently -N(R)C(=O)-, -C(=O)N(R)-, -OC(=O)-, -C(=O)O-, -O-, -S-, -S(O)-, -S(O)₂-, -N(R)-, -C(=O)-, or a direct bond; wherein each R is independently H or (C_1-C_6)alkyl.

92.

The compound of claim 91 wherein at least one of W and Q is -N(R)-.

SEARCHED - SERIALIZED - FILED - INDEXED - PAGED

93. The compound of claim 90 wherein Z and ZZ are each independently of the formula W-(CH₂)_n-Q wherein, n is between about 1 and about 20, between about 1 and about 15, between about 2 and about 10, between about 2 and about 6, or between about 4 and about 6; wherein W and Q are each independently -N(R)C(=O)-, -C(=O)N(R)-, -OC(=O)-, -C(=O)O-, -O-, -S-, -S(O)-, -S(O)₂-, -C(=O)-, -N(R)-, or a direct bond; wherein each R is independently H or (C₁-C₆)alkyl.

94. The compound of claim 93 wherein at least one of W and Q is -N(R)- wherein each R is independently H or (C₁-C₆)alkyl.

95. The compound of claim 93 wherein n is between about 2 and about 6.

96. The compound of claim 90 wherein Z separates T and the residue by about 5 angstroms to about 200 angstroms.

97. The compound of claim 90 wherein at least one of Z and ZZ is a divalent radical formed from a peptide or an amino acid.

98. The compound of claim 97 wherein the peptide comprises 2 to about 25 amino acids.

99. The compound of claim 90 wherein the peptide is poly-L-lysine, containing about 8 to about 11 residues.

100. The compound of claim 90 wherein at least one of Z and ZZ is a 1,ω-divalent radical formed from a peptide.

D6690498
11-6000

Sub A14

101. The compound of claim 90 wherein (C=O) in the group is attached to Z-T at the b-, d- or e- position.

102. The compound of claim 90 wherein at least one of T and TT is a residue of an antineoplastic agent.

103. The compound of claim 102 wherein the antineoplastic agent is a cytotoxic agent.

104. The compound of claim 103 wherein the cytotoxic agent is doxorubicin or paclitaxel.

105. A compound wherein a residue of a compound of formula I (Figure 1) is linked directly or by a linker to a residue of one or more chemotherapeutic agents; wherein X is CN, OH, CH₃, or adenosyl; wherein the compound of formula I is also linked directly or by a linker to a detectable radionuclide; or a pharmaceutically acceptable salt thereof.

106. The compound of claim 105 wherein the detectable radionuclide is linked to a residue of the b, d or e-carboxamide of the compound of formula I.

107. The compound of claim 105 wherein the detectable radionuclide is linked by a linker to a residue of the compound of formula I.

108. The compound of claim 105 wherein the detectable radionuclide is directly linked to a residue of the compound of formula I.

109. The compound of claim 105 wherein the detectable radionuclide is a non-metallic radionuclide.

110. The compound of claim 109 wherein the non-metallic radionuclide is Carbon-11, Fluorine-18, Bromine-76, Iodine-123, or Iodine-124.

111. A pharmaceutical composition comprising a compound of any one of claims 1-110 and a pharmaceutically acceptable carrier.

112. A compound of any one of claims 1-110 for use in medical therapy or diagnosis.

113. The use of claim 105 for the manufacture of a medicament for imaging a tumor in a mammal.

114. The use of claim 113 wherein the tumor is located in the breast, lung, thyroid, lymph node, kidney, ureter, bladder, ovary, teste, prostate, bone, skeletal muscle, bone marrow, stomach, esophagus, small bowel, colon, rectum, pancreas, liver, smooth muscle, brain, spinal cord, nerves, ear, eye, nasopharynx, oropharynx, salivary glands, or the heart.

115. The use of a compound of any one of claims 1-110 for the manufacture of a medicament for treating a tumor in a mammal.

116. The use of claim 115 wherein the tumor is located in the breast, lung, thyroid, lymph node, kidney, ureter, bladder, ovary, teste, prostate, bone, skeletal muscle, bone marrow, stomach, esophagus, small bowel, colon, rectum,

pancreas, liver, smooth muscle, brain, spinal cord, nerves, eye,
nasopharynx, oropharynx, salivary glands, or the heart.

117. A method of treating a tumor in a mammal in need of such treatment comprising administering to the mammal an effective amount of a compound of any one of claims 1-110.

118. The method of claim 117 wherein the tumor is located in the breast, lung, thyroid, lymph node, kidney, ureter, bladder, ovary, teste, prostate, bone, skeletal muscle, bone marrow, stomach, esophagus, small bowel, colon, rectum, pancreas, liver, smooth muscle, brain, spinal cord, nerves, ear, eye, nasopharynx, oropharynx, salivary glands, or the heart.

119. A method of imaging a tumor in a mammal in need of such imaging comprising administering to the mammal an effective amount of a compound of claim 105; and detecting the presence of the compound.

120. The method of claim 119 wherein the tumor is located in the breast, lung, thyroid, lymph node, kidney, ureter, bladder, ovary, teste, prostate, bone, skeletal muscle, bone marrow, stomach, esophagus, small bowel, colon, rectum, pancreas, liver, smooth muscle, brain, spinal cord, nerves, ear, eye, nasopharynx, oropharynx, salivary glands, or the heart.